Impaired Vasoconstriction of Peripheral Cutaneous Blood Flow in Type 1 Diabetic Patients Following Food Ingestion

M. Rossi*[1], K. Lall[2], N. Standfield[2], A. Dornhorst[1]

[1]*Department of Endocrinology, Imperial College School of Medicine, The Hammersmith Hospital, London, UK*
[2]*Department of Vascular Surgery, Imperial College School of Medicine, The Hammersmith Hospital, London, UK*

Abstract

Abnormalities in cutaneous blood flow (CBF) in otherwise healthy subjects with Type 1 diabetes mellitus (DM) have been demonstrated in response to local insults to the skin. To investigate whether defects also occurred in response to a regular daily activity, CBF was measured with laser Doppler flowmetry (LDF), before and 20 min after starting a mixed meal in 13 male Type 1 DM subjects with no clinical evidence of neuropathy, nephropathy or macroangiopathy and compared to 7 non-diabetic controls. Diabetic subjects and controls were of similar age and body mass index (mean ± SD, 33.7 ± 7.4 vs 37.1 ± 9.2 years and 25.2 ± 2.9 vs 24.5 ± 2.9 kg m^{-2}, respectively). In subjects with DM, HbA_{1c} was 8.3 ± 0.6 % (normal range 4–5.5 %) and duration of diabetes was 18 (8–38) years, median (range). Following a mixed meal the CBF fell in the controls by 36 % (24 to 56), median (range), compared to 3 % (–5 to 18) in Type 1 DM subjects, $P < 0.0005$. These results show there is a normal physiological fall in CBF following food ingestion which is attenuated in Type 1 DM. These abnormalities of vasoconstriction in the peripheral microcirculation are present after 8 years of diabetes and precede the development of clinically apparent neuropathy or vascular disease. © **1998 John Wiley & Sons, Ltd.**

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Introduction

Microvascular complications of diabetes include retinopathy, nephropathy and neuropathy, and account for much of the increased morbidity and mortality associated with diabetes. Investigations in diabetic subjects have shown microangiopathy to be a generalized process involving most capillary beds. Increases in retinal and renal blood flow have been shown early in the development of diabetes.[1,2] In the skin defects in autoregulation, the ability to keep blood flow constant in the face of changing peripheral resistance, have been demonstrated in diabetic subjects with retinopathy and nephropathy.[3] Early increases in precapillary blood flow and capillary hypertension have been postulated as causing microvascular sclerosis and this increase in blood flow has been interpreted as evidence of impaired autoregulation of the microcirculation.[4] In otherwise healthy diabetic subjects, increase in basal cutaneous blood flow (CBF) has also been described,[5] although a diminished blood flow reserve has been seen in response to local noxious stimuli such as skin warming,[6] local trauma,[7] and arterial occlusion.[8]

The present study was aimed to quantify, by means of laser Doppler flowmetry (LDF), changes in the peripheral microcirculation during food ingestion in non-diabetic subjects and to compare this with Type 1 DM subjects free from overt macrovascular or neuropathic complications. Laser Doppler flowmetry (LDF) was used as a non-invasive means of providing a real time assessment of CBF. Various techniques have been employed to detect abnormalities of CBF; of these LDF is particularly useful in providing accurate measurements of haemodynamic changes of the microcirculation.[9]

Subjects and Methods

Subjects

The subjects included 13 Type 1 DM and 7 non-diabetic adult males. Eleven of the diabetic subjects were on a

Abbreviations: CBF cutaneous blood flow; LDF laser Doppler flowmetry

*Correspondence to: Dr. M Rossi, ICSM Endocrine Unit, Francis Fraser Laboratories, Hammersmith Hospital, Du Cane Rd, London W12 0NN, UK

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basal bolus insulin regime and 2 on BD insulin. The DM subjects were recruited from the hospital diabetic outpatient department, where a detailed clinical examination was performed, including dilated fundoscopy. Glycaemic control was assessed by glycolysated haemoglobin (HbA_{1c}, non-diabetic range 4–5.5) and evidence of nephropathy using albumin/creatinine ratio measurement on a random urine sample. Subjects were chosen on the basis of being normotensive (blood pressure $<$160/90 mmHg), without proteinuria (albumin/creatinine ratio $<$0.3), peripheral vascular disease or neuropathy. The latter were assessed by the presence of palpable foot pulses, a Doppler ankle-brachial pressure ratio $>$1.0, normal ankle reflexes and preserved vibration sense at the malleoli. In addition only diabetic subjects with normal cardiovascular autonomic testing were included (see below). The controls were healthy non-diabetic hospital staff who fulfilled the above criteria. Both subjects and controls gave consent for the studies. The two groups of subjects were of similar age and BMI (Table 1).

Cardiovascular Autonomic Tests

Autonomic function was formally assessed by measuring mean heart rate variability on deep breathing and in response to standing (the 30:15 ratio) using a continuous electrocardiogram trace. Fall in systolic blood pressure was also recorded on standing. Evidence of automonic dysfunction was considered present if the heart rate variability was $<$10 beats min^{-1}, the 30:15 ratio was $<$1.04 or the fall in systolic blood pressure was $>$10 mmHg.

Laser Doppler Flowmetry

All studies were performed in a clinical investigational ward with room temperature maintained at 25°C. Both control and diabetic subjects were seated throughout the study period. Cutaneous blood flow was measured at the pulp surface of the big toe using a laser Doppler flowmeter, LDF (Moor Instruments Ltd, Axminster, Devon), which illuminates a small area of skin with monochromatic light. A photomultiplier measures the scattered light which is reflected back from the skin surface that consists of Doppler shifted light, due mainly to the movement of erythrocytes in the microcirculation, and non-shifted light from surrounding connective and stromal elements. The photomultiplier produces the laser Doppler signal, a function of both the shifted and non-shifted light, and is recorded directly into a computer with a DRTSOFT (copyright Moor Instruments Ltd) programme.

Resting laser Doppler flux was measured in arbitrary units from a calibrated zero line determined by calibration of the laser probes held in a probe holder against a uniform white surface. As laser Doppler flowmetry is influenced by changes in skin temperature,[10] the toe pulp was maintained at a constant normal skin temperature of 30°C by placing blankets over the feet to prevent heat loss. The probe itself was attached to the skin surface of the pulp of the big toe with transparent double-sided sticky tape. Initial studies on 4 control and 4 Type 1 DM subjects showed that LDF changes occurring with meals were seen in the first 20 min after taking food. LDF then returned to basal levels by 20 min after completion of the meal and remained stable during similar time periods when no food was ingested. CBF was therefore measured during the study using LDF for 10 min at rest and 30 min after starting a standardized mixed cold meal of calorific value 600–750 kcal. All meals were completed within 15 min. To assess the reproducibility of the technique 2 Type 1 DM subjects and 2 control subjects were assessed on two separate occasions at least 24 h apart.

Table 1 Details of the Type 1 DM and control subjects

	Type 1 DM subjects	Control subjects
Number	13	7
Age (yr)	33.7 ± 7.4[a]	37.1 ± 9.2[a]
BMI ($kg\ m^{-2}$)	25.2 ± 2.9[a]	24.5 ± 2.9[a]
HbA_{1c} (%)	8.3 ± 0.6[a]	
Duration of diabetes (yr)	18 (8–38)[b]	

[a]Mean ± SD.
[b]Median (range).

Statistical Analysis

Results for CBF are expressed as a percentage change of CBF from basal to 20 min after food ingestion. Values were taken as an average over a 60 s period at these time points. All normally distributed data are expressed as means ± SD and non-normally distributed data as median (range). Comparison of normally distributed data between the diabetic and non-diabetic groups was made using an unpaired Student's *t*-test, while comparison of CBF was made using the Mann-Whitney U-test. In both cases $P < 0.05$ was considered significant.

Ethical approval was obtained from the Hammersmith Hospital Trust's Ethics Committee.

Results

In the subjects with DM, mean HbA_{1c} was 8.3 % (range 7.1–9.0 %). The diabetic subjects had cardiovascular autonomic function tests within normal range.

There was a fall in CBF in response to the mixed meal in the control subjects, with a median fall of 36 % (24 to 56) (Figures 1 and 2). In contrast only 2 of the 13 DM subjects had a fall in CBF greater than 5 %, and in

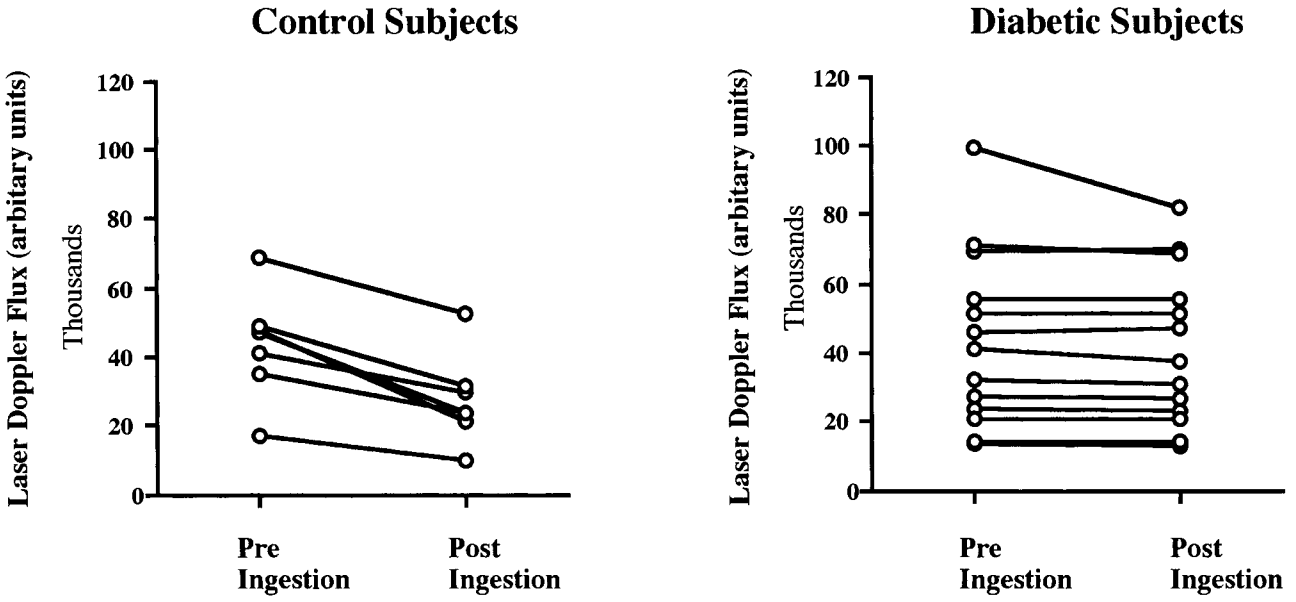

Figure 1. Comparison of laser Doppler flux measurements at the pulp surface of the big toe in control and Type 1 DM subjects pre-ingestion and 20 min after starting a mixed meal

3 subjects a paradoxical rise occurred of 1–5 % (Figure 1). The overall change in CBF 20 min after food ingestion in the diabetic group was 3 % (–5 to 18) which was significantly less than the controls, $p < 0.0005$ (Figure 2). This difference was still apparent when only the 6 diabetic subjects without retinopathy were analysed $p < 0.005$.

The change in CBF was found to be reproducible. The 2 Type 1 DM subjects were both found to vary by <4 % and the 2 control subjects studied were found to vary by <10 %.

Discussion

Feeding is associated with a physiological increase in intestinal and hepatic blood flow. These may remain elevated for 3 h postprandially, diverting regional blood flow from non-visceral tissues.[11] In the present study we observed a decrease in cutaneous blood flow in the lower limbs of non-diabetic subjects of over 30 % 20 min after starting a mixed meal. This physiological response of CBF to feeding was severely blunted in 13 Type 1 DM subjects, such that no subject had a response comparable to that seen in the controls. This demonstrates the loss of counter-regulatory control mechanisms in the peripheral microcirculation of Type 1 DM subjects.

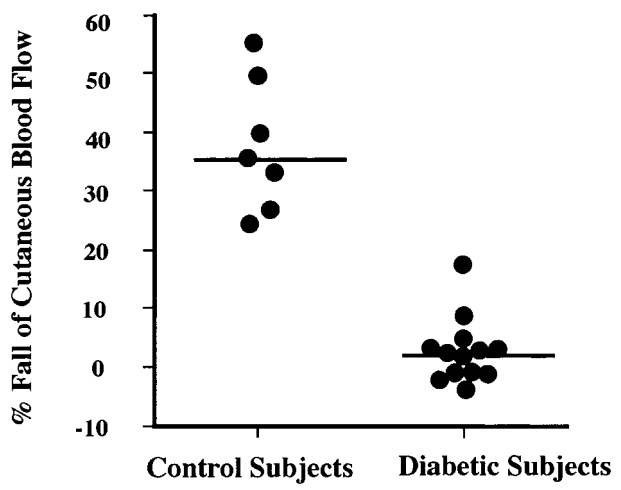

Figure 2. Scatter blot showing percentage change in fall in cutaneous blood flow in control and Type 1 DM subjects from basal to 20 min after starting a mixed meal. The horizontal line represents the median in each group. Mann-Whitney *U*-test, $p < 0.0005$

Physiological vasoconstriction of CBF in the lower limbs also occurs on standing. This has previously been shown to be attenuated in adult diabetic subjects with neuropathy when compared to controls or diabetic subjects without neuropathy.[12] Studies in post-pubertal Type 1 DM adolescents, mostly without complications, also demonstrated an attenuated vasoconstriction of CBF on standing.[13]

Although the present study does not examine why the diabetic subjects did not reduce their CBF in response to feeding, it is possible that exogenous insulin (a recognized vasodilator) was a contributing factor. A direct metabolic effect seems unlikely as the 4 subjects with excellent control ($HbA_{1c} < 7.6$ %) had a similar lack of peripheral vasoconstriction as the others in the group. The inclusion of only diabetic subjects with normal cardiovascular autonomic function tests suggests that changes in central autonomic function are not an explanation for the attenuated CBF response in the diabetic group to feeding and argues against the differences being due to delayed gastric emptying. A change in the blood glucose *per se* could also have a direct effect on cutaneous blood flow responses and could theoretically therefore be responsible for the differences seen in the diabetic and control subjects. However,

changes in CBF were occurring within the first 20 min of starting a meal and were already back to basal blood flow by 20 min after ending the meal in all cases studied, a time when blood glucose levels would still be expected to be rising. Finally, differences in skin temperature cannot explain these findings[10] as this remained similar and constant for subjects and controls.

This study highlights a daily situation in which functional abnormalities of the microcirculation are present in diabetic subjects prior to any clinical detection of perpheral vascular disease, nephropathy or neuropathy. As the magnitude of their attenuated CBF response was seen even in the patients without retinopathy, these defects in the skin microcirculation occur prior to the development of other clinical manifestations of microvascular disease.

The finger and toe pulps contain well-innervated anastomotic connections between arterioles and venules. Rapid changes at these extremities can occur, with blood flow varying between 1 and 150 ml 100 g^{-1} skin min^{-1} in response to thermoregulatory stimuli.[11] The subdermal venous capillary plexus provides not only an important blood reserve but also an easy anatomical site at which physiological responses to various stimuli can be studied. Our results are compatible with a hypothesis of structural or functional changes occurring in the microcirculation of the lower limbs, which appears to be independent of the autonomic nervous system. Diabetic subjects have been shown to have decreased distensibility of resistance vessels of the skin correlating with microvascular sclerosis and capillary basement membrane thickening.[14] Our finding of an attenuated fall in postprandial CBF may be a manifestation of these structural changes in the local vascular vessels. Alternatively these findings could result from endothelium dysfunction, since abnormalities in vascular reactivity to the potent endothelium-derived vasoconstrictor endothelin-1 have been described in diabetic subjects.[15]

In summary, this study gives further evidence that microangiopathy affects the microvascular bed of the skin in diabetic subjects. The extent to which these changes contribute to the pathogenesis of diabetic neuropathy and peripheral vascular disease remains to be investigated.

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